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No. 06-1249

IN THE

Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

On Writ of Certiorari to the Vermont Supreme Court

BRIEF OF DRI—THE VOICE OF THE DEFENSE BAR AS *AMICUS CURIAE* IN SUPPORT OF PETITIONER

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INTEREST OF *AMICUS CURIAE* DRI[1]

Amicus curiae DRI—the Voice of the Defense Bar and its members have extensive experience defending litigation implicating the Food and Drug Administration's ("FDA") expert determinations regarding prescription drugs. *Amicus* brings practical insight and real-world experiences with the substantial federal oversight of individual prescription drugs and the threats posed to public health by conflicting state co-regulation through tort law. *Amicus* will not repeat the legal arguments that are well developed by petitioner and other *amici*. Instead, *amicus* focuses the Court's attention on several key practical issues.

Despite the views of the majority below that ensuring patient safety requires state law to supplement federal drug oversight, in fact, lay fact-finders' views of complex scientific data and their focus on the allegedly injured party before them cannot substitute for—and frequently conflict with—FDA's expert determinations with respect to a particular drug. FDA is charged by Congress as the expert federal agency to examine risks and benefits at a population level far broader than the circumstances facing any individual plaintiff. The agency must balance safety across the universe of

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[1] Pursuant to Supreme Court Rule 37.6, *amicus curiae* DRI states that no counsel for any party authored this brief in whole or in part and that no entity or person, aside from *amicus curiae*, its members, and its counsel, made any monetary contribution towards the preparation and submission of this brief. Pursuant to Supreme Court Rule 37.3, counsel of record for all parties have received notice of *amicus curiae*'s intent to file this brief and have consented to the filing of this brief in letters on file with the Clerk's office.

potential patients, ensuring that beneficial drugs not only reach the market, but are accompanied by warnings that are scientifically supported and do not unnecessarily deter beneficial use. FDA considers not only patients who potentially will be harmed by use of the drug, but also patients who benefit from use and patients who would be harmed by the restriction of uses of the drug or the absence of the drug from the market altogether. Because lay fact-finders institutionally lack FDA's perspective, irreconcilable conflicts with FDA's conclusions are unavoidable and effectively allow state law to override federal law in a manner inconsistent with the federal drug system.

Amicus has first-hand familiarity with these conflicts in practice, which set up collisions between FDA decisions and state-law mandates. These conflicts leave regulated entities in an impossible position and threaten public health. Absent preemption, companies have incentives to "overwarn" to protect themselves from the threat of liability, thereby undermining FDA's goal of properly calibrating warnings to achieve optimal use; to curtail innovation; to limit availability or withdraw needed medications already on the market; and to increase prices to self-insure against litigation risks.

DRI is an international organization that includes more than 22,000 attorneys involved in the defense of civil litigation. DRI is committed to enhancing the skills, effectiveness, and professionalism of defense attorneys. Because of this commitment, DRI seeks to address issues germane to defense attorneys and the civil justice system, to promote the role of the defense attorney, to improve the civil justice system, and to preserve the civil jury. DRI has long been a voice in the ongoing effort to make the civil justice system

more fair, efficient, and—where national issues are involved—consistent. To promote these objectives, DRI participates as *amicus* in cases that raise issues of importance to its membership and to the judicial system. Recently, DRI filed an *amicus* brief in *Riegel* v. *Medtronic, Inc.*, 128 S. Ct. 999 (2008).

Here, as in *Riegel*, to allow state tort to second-guess the very expert determinations reached by FDA about what labeling is appropriate for prescription drugs would be to disrupt the efficient and fair administration of justice. Permitting States—and lay fact-finders—to serve as quasi-regulators able to require additional warnings inconsistent with FDA's own judgments creates irreconcilable conflicts with federal law and thwarts the attainment of important public health objectives.

SUMMARY OF THE ARGUMENT

First, the analysis of the court below ignores the drug-specific determinations FDA makes in exercise of its role as the expert federal agency. This error, in turn, overlooks the conflicts with federal law and the impossible situations faced by FDA-regulated entities that arise when jurors are told, as they were here, that even when FDA has determined safety and labeling issues, "we don't rely on the FDA to . . . make the safe[ty] decision" or to determine "the extent to which [a company] should have warned" because "FDA doesn't make the decision, you do." JA 211-12, 217. This approach is demonstrably false and irreconcilable with congressional design.

Second, by permitting such second-guessing through state law, the court below ignores well-established principles recognizing that courts are not well-suited to reevaluate decisions within an agency's expert discretion. Moreover, it poses special dangers

given that lay jurors make poor substitutes for FDA in this context because FDA, as the expert federal agency, must make nuanced scientific judgments and set consistent nationwide policy based on overall societal benefits and risks, rather than those implicated in the case of a single litigant.

Third, the absence of preemption encourages numerous negative effects, including (1) increasing defensive labeling to the detriment of optimal patient care, (2) discouraging manufacturers from bringing needed medications to market for fear of liability, (3) encouraging manufacturers to withdraw needed medications from the United States market even though they are available abroad, and (4) increasing prices for those drugs that remain on the market.

ARGUMENT

I. LITIGATING PRESCRIPTION DRUG LABELING ISSUES FDA ALREADY HAS RESOLVED INTERFERES WITH FDA'S FEDERAL MANDATE AND LEAVES REGULATED ENTITIES IN AN IMPOSSIBLE POSITION.

Unacknowledged in the opinion below are the scope and depth of federal regulation to which prescription drugs are subjected under FDA's federal mandate. Cf. Pet. App. 5a; *id.* at 17a. Where (as here) FDA has addressed a specific risk issue, state-law efforts to supplant that determination conflict with FDA's federal mandate and interfere with its mission. Absent preemption, regulated entities are left in an impossible position between dueling federal and state law obligations.

A. FDA, The Expert Federal Agency, Is Charged By Congress With Exclusively And Extensively Regulating Prescription Drugs And Their Risks.

1. Since the Pure Food and Drug Act of 1906, Congress has charged FDA, and its predecessor agencies, with regulating drugs in the United States. The scope of FDA's oversight has increased over time.[2] Through the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 *et seq.* ("FDCA"), Congress has charged FDA as the exclusive "expert agency" to regulate every aspect of prescription drugs. *Weinberger* v. *Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 619, 627 (1973); see 21 U.S.C. § 393(b) (requiring FDA to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner" and to "protect the public health by ensuring that . . . drugs are safe and effective" as labeled).

Before a prescription drug may be marketed in the United States, FDA must approve a new drug

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[2] In 1938, federal law first required pre-market applications for new drugs. *See* Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, § 505, 52 Stat. 1040, 1052-53 (1938); *United States* v. *Generix Drug Corp.*, 460 U.S. 453, 458 (1983). In 1962, federal law was expanded to prohibit the distribution of a new drug in interstate commerce unless FDA had affirmatively found the drug safe and effective. *See* Drug Amendments Act of 1962, Pub. L. No. 87-781, sec. 102, § 201, 76 Stat. 780, 781-82; Michael I. Krauss, *Loosening the FDA's Drug Certification Monopoly: Implications for Tort Law and Consumer Welfare*, 4 Geo. Mason L. Rev. 457, 461-62 (1996). Thus, unlike the regulation of most other products, "after 1962 a central regulatory authority, rather than the market choices of suppliers, physicians, and patients, determined which drugs were desirable or undesirable." *Id.* at 462.

application ("NDA"). 21 U.S.C. § 355(a), (b). This approval is granted only after FDA is satisfied that the drug is "safe" and "effective." *Id.* § 355(b)(1). An NDA is the culmination of many years of research and evaluation, including laboratory research, animal testing, and multiple phases of clinical studies. See generally Ctr. for Drug Evaluation and Research ("CDER"), Dep't of Health & Human Servs. ("HHS"), FDA, *The CDER Handbook* 4-20 (1998), *available at* http://www.fda.gov/cder/handbook. An NDA contains thousands of pages of medical, pharmacology, chemistry, biopharmaceutical, and statistical submissions. See *id.* at 19, 21; 21 C.F.R. § 314.50 (outlining required NDA contents).

FDA conducts a "strict and demanding" review of these submissions, *Weinberger*, 412 U.S. at 619, 627, conducting a "comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling." FDA, Requirements on Content and Format of Labeling for Human Prescription Drugs and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006). In so doing, FDA utilizes interdisciplinary teams of internal experts to make the requisite safety and efficacy determinations across a number of complex disciplines. For example, medical officers (mostly physicians) evaluate clinical testing, animal toxicology, and human pharmacology. *CDER Handbook*, *supra*, at 22. Pharmacokineticists analyze how a drug's active ingredients are metabolized. See *id.* at 23. Statisticians assess data underlying studies, study methodology, and whether and how study findings can be extrapolated to nationwide patient populations. *Id.*

In addition, advisory panels of outside scientists provide "wider national expert input" into FDA's drug

approval decisions. *Id.* Panels must include scientists "qualified by training and experience to evaluate the safety and effectiveness of the drugs . . . and . . . to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs." 21 U.S.C. § 355(n)(3). Panelists must possess "diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions." *Id.* (at least two panelists must be "specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated"). Panels also must include "a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel." *Id.*

An essential aspect of an NDA submission, and FDA's review, is the proposed product labeling. *Id.* § 355(b)(1)(F). Labeling contains not only basic information about dosage and drug composition, but also detail about the disease or health condition for which the drug is intended, methods of administration, and information about risks. 21 C.F.R. § 201.57. Final approved labeling "communicates the conclusions of FDA['s] review of the data." FDA, Professional Product Labeling, Meeting Notice, 60 Fed. Reg. 52,196, 52,196 (Oct. 5, 1995). It "reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively," and accordingly constitutes "[t]he centerpiece of risk management for prescription drugs generally." 71

Fed. Reg. at 3934; see also 21 C.F.R. § 201.56(a) ("labeling must contain a summary of the essential scientific information needed for the safe and effective use of the drug[,] labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular[,] labeling must be based whenever possible on data derived from human experience").

FDA approves an NDA and draft labeling only after it is satisfied that the applicant has met statutory standards for safety and effectiveness under labeled conditions of use. 21 U.S.C. § 355(d); 21 C.F.R. § 314.105(c). If FDA concludes that these showings are insufficient, or that the labeling "is false or misleading in any particular," then the agency "shall issue an order refusing to approve" the NDA. 21 U.S.C. § 355(d); 21 C.F.R. § 314.125(b).

2. If FDA grants approval, the agency remains active in evaluating the drug's safety and efficacy as labeled, after it reaches the market. The agency has broad powers to revoke approval if new clinical trials or other scientific data reliably demonstrate that the drug no longer offers sufficient assurance of safety or effectiveness as labeled. 21 U.S.C. § 355(e).[3] FDA has asserted authority to require, as a condition of

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[3] FDA has withdrawn or suspended drug approvals on numerous occasions. *See*, *e.g.*, FDA, *FDA Data on PDUFA Drug Approvals, Safety Withdrawals & New Boxed Warnings*, *at* http://www.fda.gov/oc/pdufa/FDADrugAppSafetyData_files/NMESafetySumm.html (last visited May 28, 2008) (FDA ordered 11 safety-based withdrawals of drugs whose applications were received between 1993 and 2004). FDA also has requested changes in drug labeling based on post-marketing data on numerous occasions. *See*, *e.g.*, *id.* ("Black Box" warnings, the most severe type of warning, added to 29 drugs in the same period).

NDA approval, that manufacturers conduct post-marketing studies regarding "risks, benefits, and optimal use." 21 C.F.R. § 312.85; see Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices*, 48 Rutgers L. Rev. 883, 914 n.126 (1996) ("Once comparatively rare, post-marketing surveillance studies—sometimes known as Phase IV testing—have now become the rule."). Additionally, manufacturers are required to review and file reports of "[a]dverse drug experience[s]," broadly defined as "[a]ny adverse event associated with the use of a drug in humans, whether or not considered drug related." 21 C.F.R. § 314.80. Companies also must file regular reports of other field experiences and any information that "might affect the safety, effectiveness, or labeling of the drug." *Id.* § 314.81(b)(2)(i). In addition, citizens may provide their views to FDA for consideration.[4]

Nothing in the FDCA or FDA's interpretations of the statutory and regulatory regime supports the view expressed by the court below that a manufacturer may make "unilateral changes to drug labels whenever [it] believes [the changes] will make the product safer." Pet. App. 13a; *accord* Br. United States on Petition, 2007 WL 4555760, at *12-14

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[4] *See*, *e.g.*, 21 C.F.R. § 10.30 (establishing process for citizens to petition the agency to "issue, amend, or revoke a regulation [or] order [or] take or refrain from taking any other form of administrative action"); *cf. Henley* v. *FDA*, 873 F. Supp. 776, 780-86 (E.D.N.Y. 1995) (holding FDA did not act arbitrarily or capriciously in denying citizen's petition seeking to require warnings that the drugs in question "'may cause cancer in humans,'" and recognizing that "FDA's determination of what labeling best reflects current scientific information regarding the risks and benefits of [the drugs] involves a high degree of expert scientific analysis"), *aff'd*, 77 F.3d 616 (2d Cir. 1996).

(rejecting view of the court below). To the contrary, "[s]ubstantive changes in labeling . . . are more likely than other changes to affect the agency's previous conclusions about the safety and effectiveness of the drug." FDA, New Drug and Antibiotic Regulations, 50 Fed. Reg. 7452, 7470 (Feb. 22, 1985). Accordingly, in general, post-marketing labeling changes may only be made after FDA approval. See 21 C.F.R. § 314.70(b)(2); see also *id.* § 201.57(c) (outlining criteria for labeling changes). As a narrow exception to this rule, if the manufacturer becomes aware of "newly discovered risks" of sufficient scientific heft, FDA, New Drug and Antibiotic Regulations, 47 Fed. Reg. 46,622, 46,623 (proposed Oct. 19, 1982), it may submit a supplement to the agency while changing the labeling, see 21 C.F.R. § 314.70(c)(6)(iii); FDA, Supplemental Applications Proposing Labeling Changes for Approved Drugs, Biologics, and Medical Devices, 73 Fed. Reg. 2848, 2848 (proposed Jan. 16, 2008) (noting "agency's longstanding view" that changes may be made without prior FDA approval only for "newly acquired information" with "sufficient evidence of a causal association with the drug"). In contrast, where (as here) no newly discovered risks are at issue, the manufacturer must go through the pre-approval process before making a change. See 47 Fed. Reg. at 46,623, 46,625; 73 Fed. Reg. at 2848; *accord* Br. United States on Petition, 2007 WL 4555760, at *14-15 (recognizing no new risk information exists in this record).

Even when a manufacturer believes an immediate change in labeling is appropriate based on newly discovered risk information, FDA still can reject the proposed change based on its review of the science or the regulatory balance it seeks to achieve in the labeling. 21 C.F.R. § 314.70(c)(7). The agency may

order the company to discontinue distribution, *id.*, and the manufacturer may be charged with distributing a "misbranded" drug, 21 U.S.C. § 331(a)-(b); see Br. United States on Petition, 2007 WL 4555760, at *15. A drug is misbranded, *inter alia*, when the "labeling is false or misleading in any particular." 21 U.S.C. § 352(a). Misbranding may occur both where labeling fails to *include* warnings FDA has found warranted, and where the labeling fails to *exclude* warnings that do not meet FDA's standards. See *id.* § 352(a), (f); 73 Fed. Reg. at 2850 ("Federal law governs not only what information must appear in labeling, but also what information may not appear."); *Colacicco* v. *Apotex Inc.*, 521 F.3d 253, 269 (3d Cir. 2008) (holding additional warnings sought by plaintiffs were "without scientific basis" and "would therefore be false and misleading" in violation of federal misbranding law); 71 Fed. Reg. at 3935 ("[A]dditional disclosures of risk information can expose a manufacturer to liability under the [FDCA] if the additional statement is unsubstantiated or otherwise false or misleading.").

"Misbranding" is a "prohibited act" under the FDCA, 21 U.S.C. § 331, and the consequences of misbranding can be considerable, including "serious criminal and civil penalties," *Abbott Labs.* v. *Gardner*, 387 U.S. 136, 153 (1967), *abrogated on other grounds by*, *Califano* v. *Sanders*, 430 U.S. 99 (1977); see 21 U.S.C. § 355(e) (withdrawal); *id.* §§ 332-334 (criminal penalties, injunctions, and seizure). Given these risks, "manufacturers typically consult with the FDA before making a label revision." *In re Bextra & Celebrex Mktg. Sales Pracs. & Prod. Liab. Litig.*, No. 05-1699, 2006 WL 2374742, at *8 (N.D. Cal. Aug. 16, 2006) (Breyer, J.); see Br. United States on Petition, 2007 WL 4555760, at *15 (explaining that "[f]or these

reasons, in practice manufacturers typically consult with FDA before making labeling changes that the manufacturer believes could appropriately be made unilaterally").

3. Recent legislation further enhances and formalizes FDA's already robust post-market powers. See Food and Drug Administration Amendments Act of 2007 ("FDAAA"), Pub. L. No. 110-85, 121 Stat. 823, 823 ("An Act to amend the [FDCA] . . . to enhance the postmarket authorities of the [FDA] with respect to the safety of drugs . . . ."); 73 Fed. Reg. at 2850 (FDAAA "provide[s] streamlined authority for FDA to respond to new and emerging safety information"). For instance, FDAAA expressly authorizes FDA to require "postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug" to address already-known risks, risk signals, and unexpected risks. 21 U.S.C. § 355(o)(3)(A)-(B). It also enhances FDA's power to require labeling changes based on "new safety information that [it] believes should be included in the labeling." *Id.* § 355(o)(4)(A); *accord* 73 Fed. Reg. at 2850 (FDAAA "confirm[s] that Congress intends FDA to carefully regulate the content of labeling for approved products" and allows FDA "to rapidly amend the labeling").

To fund FDA's expanded drug approval and post-market surveillance, FDAAA also substantially increases existing user fees. See Pub. L. No. 110-85, sec. 103(b), § 736(b), 121 Stat. at 827 (authorizing $392 million in user fees, an increase of $87 million from the previous year).[5] These fees allow FDA to

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[5] Since 1992, the Prescription Drug User Fee Act ("PDUFA") has authorized FDA to collect user fees to increase the speed of NDA review and to expand post-market risk management.

hire more reviewers and engage in even more rigorous post-marketing surveillance. See, *e.g.*, Tomas J. Philipson et al., Nat'l Bureau of Econ. Research, Working Paper No. 11724, *Assessing the Safety and Efficacy of the FDA: The Case of the Prescription Drug User Fee Acts* (Oct. 2005), *available at* http://www.nber.org/papers/w11724 (finding user fee regime saves 124,000 to 254,000 life-years).

In implementing FDAAA, FDA recently launched the Sentinel System, "a national, integrated, electronic system for monitoring medical product safety." FDA, *Sentinel System to Monitor Medical Product Safety* (May 22, 2008), *available at* http://www.fda.gov/consumer/updates/sentinel052208.pdf. This system further expands agency access to databases run by private health plans, insurers, and government agencies, thereby enhancing its ability to observe and respond to potential safety issues. See FDA, *The Sentinel Initiative: National Strategy for Monitoring Medical Product Safety* 4, 18-24 (May 2008), *available at* http://www.fda.gov/oc/initiatives/advance/reports/report0508.pdf; News Release, HHS, New Efforts to Help Improve Medical Products for Patient Safety and Quality of Medical Care (May 22,

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Andrew C. von Eschenbach, *Commissioner's Report of FDA, HHS, FY 2006 Performance Report to the President and the Congress for PDUFA* (2006) *available at* www.fda.gov/ope/pdufa/report2006/PDUFA2006perf.pdf. FDA reports that user fees have been "instrumental in new drugs reaching consumers in a timelier manner" and are "essential to maintain the resources required to sustain the advances made in FDA review performance." *Id.* PDUFA has been reauthorized three times by Congress with overwhelming support. *See*, *e.g.*, H.R. Res. 3580, 110th Cong. (2007); 153 Cong. Rec. H10599 (daily ed. Sept. 19, 2007) (third reauthorization passes House 405-7); 153 Cong. Rec. S11841 (daily ed. Sept. 20, 2007) (third reauthorization passes Senate by unanimous consent).

2008), *available at* http://www.hhs.gov/news/press/2008pres/05/20080522a.html (system enhances "proactive surveillance of medical products on the market").

B. FDA's Determinations About Individual Prescription Drugs Make Conflicts With State Law Inevitable.

Applied to individual drugs, these regulatory principles require a series of delicate public health calibrations by FDA. "FDA is challenged to make sure that it consistently balances access and innovation against the steps taken to improve [its] approach to safety issues." FDA, *The Future of Drug Safety—Promoting and Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report* 3 (Jan. 2007), *available at* http://www.fda.gov/oc/reports/iom013007.pdf. FDA's dual mission—minimizing risks *and* facilitating access—necessarily involves the exercise of expert judgment because every drug has risks. See 21 U.S.C. § 393(b).

To fulfill its mission, FDA must make labeling decisions regarding individual drugs that require the agency to rely on its expertise and knowledge of the total public health picture. The agency makes a "comprehensive scientific evaluation of the product's risks and benefits *under the conditions of use*"—not in the "abstract." 71 Fed. Reg. at 3934 (emphasis added). For instance, the agency may be willing to tolerate significant risks when a drug may be the only viable treatment for a life-threatening condition. See *United States* v. *Rutherford*, 442 U.S. 544, 556-57 (1979) (recognizing that the balance the agency seeks to strike between effectiveness and safety may vary according to the condition the drug is intended to treat); *accord* Br. United States on Petition, 2007 WL 4555760, at *10 (FDA has approved "highly toxic"

and "not 'safe'" cancer treatments "because the potential benefits to health outweigh the risks"); 21 C.F.R. pt. 314 subpt. H.

These dynamics translate directly into FDA's determinations about proper drug labeling. The agency must craft balanced labeling that both ensures prescribing physicians understand the dangers of the medication and its benefits, thereby allowing them to select the proper course of treatment for individual patients, without overwhelming them with low-risk information that undermines rational prescribing. As FDA has explained, "[o]verwarning, just like underwarning, can . . . have a negative effect on patient safety and public health" because "theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance." 71 Fed. Reg. at 3935 (internal quotation omitted).

In reaching these decisions, FDA must exercise its considerable expertise and discretion to reach the decision it finds most appropriate in light of all the circumstances. *Id.* at 3934 (FDA considers "important and practical public health issues pertaining to the use of the product in day-to-day clinical practice"). As part of this process, there may be a divergence of opinion among FDA reviewers. FDA, *Guidance: Drug Safety Information—FDA's Communication to the Public* 4 (Mar. 2007), *available at* http://www.fda.gov/CDER/guidance/7477fnl.pdf (acting on emerging risks is "a matter of judgment, about which reasonable people with relevant experience may disagree"). For instance, a medical officer may recommend one course of action based on her review in a given discipline that the agency ultimately disagrees with after reviewing the entire picture. Likewise, advisory boards may have

dissenting voices and sometimes recommend action the agency ultimately rejects. See Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 Va. L. Rev. 1753, 1781 n.86 (1996) (although FDA "usually accepts [advisory committee advice] regarding the approval of new drugs[,] [a]n advisory committee can, and some occasionally do, disagree with the assessment of the agency's own reviewers about the approvability of a drug"). To achieve the goals of the FDCA, however, final decisions which will guide drug availability, labeling, and use nationwide ultimately must be reached by the agency. Cf. *id.* ("these committees offer only advice; they do not make decisions"). The highly deferential FDCA scheme designed by Congress necessarily means that, in the end, FDA alone must decide and strike these balances.

Where, as here, state law runs headlong into the federal agency's judgment, the regulated entity faces an inevitable Catch-22. Its products may not reach or remain on the market if it fails to abide by FDA's judgments or if it substitutes its own views of the science and proper labeling for that of the agency. The company also faces the prospect of federal penalties should it decide to distribute a misbranded drug in its effort to avoid state-law liability. On the other hand, engaging in federally approved conduct that is found to violate state law makes the regulated entity's product a magnet for state-law litigation. Yet, absent preemption, when FDA has made a determination about whether a drug should come to market, and has addressed a particular risk issue, state-law efforts will be permitted to override the expert agency's determinations.

II. JUDGES AND JURIES ARE NOT PROPERLY EQUIPPED TO MAKE THE JUDGMENTS CONGRESS DELEGATED TO THE EXPERT AGENCY.

As difficult as it may be for FDA to calibrate the right balance in a particular case, it is practically impossible for courts and juries to do so given that they lack the agency's knowledge and expertise, as well as its perspective.

A. Courts Routinely Defer To Expert Regulators.

Congressional design requires federal courts—never mind state law and state lay juries—to accept and defer to FDA's expert judgment and exercise of discretion about such difficult issues. See, *e.g.*, *Brandenfels* v. *Heckler*, 716 F.2d 553, 555 (9th Cir. 1983) ("Determining reliable scientific data is not the judicial function. Congress vested that responsibility in the FDA and we will not preempt its presumed expertise."); *Premo Pharm. Labs., Inc.* v. *United States*, 629 F.2d 795, 803 (2d Cir. 1980) ("FDA . . . as distinguished from a court, possesses superior expertise, usually of a complex scientific nature"); see also *Slater* v. *Optical Radiation Corp.*, 961 F.2d 1330, 1333 (7th Cir. 1992) (Posner, J.) (observing that "FDA decided, *whether rightly or wrongly*" that a product should come to market with certain warning, "but pursuant to regulations the validity of which the plaintiff does not question," plaintiffs' claims invite "a direct collision with federal policy") (emphasis added); cf. *Heckler* v. *Chaney*, 470 U.S. 821, 837-38 (1985) (holding that FDA's decisions regarding enforcement of FDCA are not subject to judicial review). Indeed, the Court has observed that "[i]t is enough for us that the expert agency . . . has determined that such regulation is desirable for the public health, for we

are hardly qualified to second-guess the Secretary's medical judgment." *United States* v. *An Article of Drug . . . Bacto-Unidisk . . .*, 394 U.S. 784, 791-92 (1969).

These principles, of course, are consistent with a body of this Court's precedents in related contexts which admonish courts not to second-guess decisions within an agency's expert discretion. As the Court explained in *United States* v. *Varig Airlines*, 467 U.S. 797 (1984), for instance:

> Decisions as to the manner of enforcing regulations directly affect the feasibility and practicality of the Government's regulatory program; such decisions require the agency to establish priorities for the accomplishment of its policy objectives by balancing the objectives sought to be obtained against such practical considerations . . . . Judicial intervention in such decisionmaking through private tort suits would require the courts to "second-guess" the political, social, and economic judgments of an agency exercising its regulatory function.

Id. at 820; see, *e.g.*, *Mobile Oil Exploration & Producing S.E. Inc.* v. *United Distrib. Cos.*, 498 U.S. 211, 231 (1991) ("We are neither inclined nor prepared to second-guess the agency's reasoned determination in this complex area."); *American Textile Mfgs. Inst., Inc.* v. *Donovan*, 452 U.S. 490, 523 (1981) ("'the possibility of drawing two inconsistent conclusions from the evidence does not prevent an administrative agency's finding from being supported by substantial evidence'") (citation omitted).[6]

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[6] *See also*, *e.g.*, *Sierra Club* v. *EPA*, 353 F.3d 976, 992 (D.C. Cir. 2004) ("We will not second-guess the agency's weighing of costs and benefits.") (Roberts, J.) (internal quotation and

Given the recognition that federal courts should not second-guess complex federal agency determinations, as addressed next, the risks associated with having state fact-finders rebalance or reject FDA's determinations under color of state law is even greater. And where, as here, a state ruling speculates why the agency acted as it did as a means to overrule FDA's decisions, the conflict and interference with the agency's functions are particularly acute. See Pet. App. 4a-5a (viewing FDA's "'brief comment[s]'" as insufficient to support its determinations).

B. Juries Are Poor Substitutes For FDA In This Context.

A dramatic gulf separates the competence of FDA from that of state jurors who, absent preemption, are called on to "police" prescription drugs and second-guess federal regulators. Laypersons applying state law cannot substitute for FDA, the expert agency congressionally delegated the role of meticulously balancing nuanced and sometimes competing nationwide goals. FDA's regulation of prescription drugs is, as shown above, governed by a sweeping network of federal law individually applied to each

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alteration omitted); *Southwestern Pa. Growth Alliance* v. *Browner*, 121 F.3d 106, 117 (3d Cir. 1997) (Alito, J.) ("It is not the role of a reviewing court to second-guess the scientific judgments of the [agency].") (internal quotation omitted); *United Steelworkers of Am.* v. *Marshall*, 647 F.2d 1189, 1206-07 (D.C. Cir. 1980) (Wright, J.) (recognizing that agency decisions turn on "inferences from complex scientific and factual data," and "we do not pretend to have the competence or the jurisdiction to resolve technical controversies in the record"); *id.* at 1263 ("Where the agency presents scientifically respectable evidence which the petitioner can continually dispute with rival . . . evidence . . . the court must not second-guess the particular way the agency chooses to weigh the conflicting evidence or resolve the dispute.").

drug. A lay jury lacks the expertise and the broader perspective of FDA and thus cannot adequately adjudicate individual patient risks in the context of population benefits—quintessentially the kind of issue FDA must confront every day. Without preemption, however, state juries are asked to do just that. See, *e.g.*, Pet. Br. 23 ("'Thank God we don't rely on the FDA to . . . make the safe[ty] decision. You will make the decision.'") (quoting JA 211).

As detailed above, FDA determinations about how best to regulate a specific drug and its labeling are highly complex. See generally, *e.g.*, *Henley* v. *FDA*, 77 F.3d 616, 620 (2d Cir. 1996) ("FDA's determination of what labeling best reflects current scientific information regarding the risks and benefits of [a drug] involves a high degree of expert scientific analysis.") (internal quotation omitted); see *supra* § I. When these issues are put to a jury, the risk of error is high. Not only do jurors lack scientific and regulatory expertise, they lack the comprehensive data necessary to assess individual patient risks in the light of the benefits a drug confers on the larger population.

As a general matter,

> the tort system, as part of a larger regulatory scheme, is best equipped to handle products or services *that do not involve intrinsic risks*, which can be predicted and regulated beforehand by legislatures, but that encompass episodic risks or faulty behavior that can only be detected after-the-fact by those personally affected by such behavior.

Alan L. Calnan, *Distributive & Corrective Justice Issues In Contemporary Tobacco Litigation*, 27 Sw. U. L. Rev. 577, 636 (1998) (emphasis added). Thus, in

prescription drug cases, which by definition involve inherent risks, juries are particularly poor substitutes for federal regulators.

Jurors also lack the nationwide perspective FDA brings to its extensive regulation of prescription drugs. As Judge Easterbrook has explained: "Jurors see today's injury; persons who would be injured if [the product were not on the market as constituted] are invisible. Although witnesses may talk about them, they are spectral figures, insubstantial compared to the injured plaintiff, who appears in the flesh." *Carroll* v. *Otis Elevator Co.*, 896 F.2d 210, 216 (7th Cir. 1990) (Easterbrook, J., concurring). A further complication is that jurors may be "prone to hindsight bias, believing that an event that has already occurred was more likely to have happened than was true *ex ante* and could have been foreseen." Hugo M. Mialon & Paul H. Rubin, *The Economics of the Bill of Rights*, 10 Am. L. & Econ. Rev. 1, app. B at 54 (2008).

Whereas FDA evaluates the risks of harm against the benefits of use in the overall population, jurors may tend to "over-assess low-probability events and are particularly likely to focus on the worst-case scenario." W. Kip Viscusi, *Jurors, Judges, and the Mistreatment of Risk by the Courts*, 30 J. Legal Stud. 107, 111 (2001); *id.* at 111-15; see also W. Kip Viscusi, *Corporate Risk Analysis: A Reckless Act?*, 52 Stan. L. Rev. 547, 588 (2000) (explaining that some jurors believe cost-benefit assessments are improper).

As Justice Breyer stated to plaintiffs' counsel during a recent oral argument:

> You came up and began and said this drug has side effects that hurt people. And that's a risk

> when you have a drug, and it's a terrible thing if the drug hurts people.
>
> There's a risk on the other side. There are people who are dying or seriously sick, and if you don't get the drug to them they die. So there's a problem. You've got to get drugs to people and at the same time the drug can't hurt them.
>
> Now, *who would you rather have make the decision as to whether this drug is, on balance, going to save people or, on balance, going to hurt people? An expert agency, on the one hand, or 12 people pulled randomly for a jury rol[l] who see before them only the people whom the drug hurt and don't see those people who need the drug to cure them?*

Warner-Lambert Co. v. *Kent*, No. 06-1498, 2008 WL 495030, at *30 (U.S. Feb. 25, 2008) (emphasis added). In the same vein, "[a]pplication of broad liability rules and the application of 20-20 hindsight often places juries in the position of second guessing the FDA on the types of warnings that should be provided with prescription drug products and which products should be marketed. Too often these judgments collide." W. Kip Viscusi et al., *Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense*, 24 Seton Hall L. Rev. 1437, 1467-68 (1994); see, *e.g.*, David R. Geiger & Mark D. Rosen, *Rationalizing Product Liability for Prescription Drugs: Implied Preemption, Federal Common Law, and Other Paths to Uniform Pharmaceutical Safety Standards*, 45 DePaul L. Rev. 395, 396-97 (1996) (discussing "retrospective jury nullification" of FDA regulations being "contrary to public policy").

Whereas jurors not only lack a sense of the overall regulatory policy a statutory scheme seeks to achieve, and "may become fixated on awarding compensation to the needy plaintiff put before them," FDA's determinations can and must "tak[e] a broader view of the inevitable tradeoffs involved in specifying appropriate product designs and disclosures of risk information." Lars Noah, *Rewarding Regulatory Compliance: The Pursuit of Symmetry in Products Liability*, 88 Geo. L.J. 2147, 2163 (2000). In sum, jury trials do not permit lay fact-finders to see the overall picture FDA must consider when striking the proper balance in regulating a particular drug. When a jury's view is substituted for FDA's, as the court below allowed, a core aspect of the federal regulatory scheme—one critical to innovation and overall public health benefits—is lost.

C. Experience Shows That, Absent Pre-emption, Lay Fact-finders May Disrupt The Careful Balances Struck By FDA.

Recently, and with seemingly increasing frequency, plaintiffs have sought to recalibrate through state law FDA's decisions about the presentation of risk information in labeling, among other agency determinations under the FDCA. Where, as here, plaintiffs' claims ask a jury applying state law to pass on the very issues addressed by FDA under federal law, those claims amount to a frontal attack on FDA's regulatory authority. State-law liability also results in a disparate state-by-state hodgepodge of duties and creates unavoidable conflicts as manufacturers attempt simultaneously to satisfy state and federal law. Recent cases illustrate the point.

1. Litigation over warnings in labeling for antidepressant drugs known as selective serotonin reuptake inhibitors ("SSRIs") illustrates the

importance of expert oversight in regulating prescription drugs, including how FDA's study of risk may unfold, how FDA ensures risk information is supported by reliable science, and how the agency provides risk information provided to prescribing physicians through labeling without improperly discouraging the use of these important products. They also demonstrate how state law threatens these federal determinations.

The main state-law claim in the SSRI litigation is that manufacturers should be held liable because "the drugs' labeling failed to warn of their association with an increased risk of suicidality" in adults. *E.g.*, *Colacicco*, 521 F.3d at 256.[7] FDA repeatedly has reviewed this risk. See *id.* at 269. In 1991, after evaluating whether SSRIs "caused or intensified suicidal thoughts," FDA's Psychopharmacological Drugs Advisory Committee concluded that "no" suicidality warning should be added to the labeling for SSRIs. *Id.*; see *Dobbs* v. *Wyeth Pharms.*, 530 F. Supp. 2d 1275, 1282-83 (W.D. Okla. 2008). Thereafter, FDA rejected citizen petitions seeking to withdraw approval "as a result of its asserted association with suicide or to include a suicide warning on the labeling of [the] drug," concluding that scientific evidence did not support this action. *Colacicco*, 521 F.3d at 269; see *Dobbs*, 530 F. Supp. 2d at 1282-83. See also *Colacicco*, 521 F.3d at 270

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[7] *Accord Dobbs* v. *Wyeth Pharms.*, 530 F. Supp. 2d 1275, 1277 (W.D. Okla. 2008); *Tucker* v. *SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL, 2007 WL 2726259, at *1 (S.D. Ind. Sept. 19, 2007); *Estates of Tobin ex rel. Tobin* v. *SmithKline Beecham Pharms.*, 164 F. Supp. 2d 1278, 1287 (D. Wyo. 2001); *Motus* v. *Pfizer Inc.*, 127 F. Supp. 2d 1085, 1086-87 (C.D. Cal. 2000).

(*amicus* briefs reiterating this point); *Dobbs*, 530 F. Supp. 2d at 1283-84 (same).

In late 2003, FDA issued a Public Health Advisory regarding increased suicidality in *pediatric* users of antidepressants and reaffirmed that there was "'no evidence'" of increased suicidality in adults. *Colacicco*, 521 F.3d at 270. In 2004, FDA conducted further studies on pediatric suicidality, finding a "causal link between the use of antidepressants and suicidality in pediatric patients," and adding a black box warning to SSRI labeling regarding pediatric use. *Tucker* v. *SmithKline Beecham Corp.*, No. 1:04-cv-1748-DFH-WTL, 2007 WL 2726259, at *3 (S.D. Ind. Sept. 19, 2007); *Colacicco*, 521 F.3d at 270-71. FDA also reviewed whether there was any increased risk in adults despite its earlier findings to the contrary. *Tucker*, 2007 WL 2726259, at *4. In 2007, it concluded that there was an increased risk of suicidality in "'children, adolescents, and young adults'" taking antidepressants, *Dobbs*, 530 F. Supp. 2d at 1284, but *no* increased risk in adults beyond age 24; indeed, "there was a reduction in risk with antidepressants compared to placebo in adults aged 65 or older," *Tucker*, 2007 WL 2726259, at *4.

Despite FDA's determinations, lawsuits nationwide have asked courts and juries to reach contrary determinations under state law. Many courts have rejected these claims on the basis of preemption. See, *e.g.*, *Colacicco*, 251 F.3d at 271; *Dobbs*, 530 F. Supp. 2d at 1290 ("the label warning that Plaintiff seeks to require has been considered and rejected by the FDA; therefore, Defendant would face conflicting obligations under Oklahoma and federal law") (footnote omitted); *Tucker*, 2007 WL 2726259, at *10. Nonetheless, other courts have allowed claims to survive summary judgment, see *Motus* v. *Pfizer Inc.*,

127 F. Supp. 2d 1085, 1092-1100 (C.D. Cal. 2000), and even to serve as the basis for substantial jury awards, see *Estates of Tobin ex rel. Tobin* v. *SmithKline Beecham Pharms.*, 164 F. Supp. 2d 1278, 1280-81, 1283-84 (D. Wyo. 2001) (upholding $6 million jury award because "the absence of warnings" regarding adult suicidality "proximately caused the murders and suicide in this case"). Indeed, the *Tobin* court permitted a multi-million dollar verdict based on the notion that SSRI use caused a murder-suicide even though the individual who allegedly killed himself and murdered his family was 60 years old—the very age group FDA had concluded has *no* increased risk of suicidality from SSRIs. See *Paxil Maker Ordered to Pay $8 Million: Jury Says Anti-Depressant Largely to Blame for Deadly Shooting Spree*, AP Online, June 6, 2001.

These outcomes cannot be squared with FDA's scientific determinations and its role as the expert agency under the FDCA. When a lay jury is permitted to substitute its own conclusions for that of the agency, certainty is undermined and the most restrictive state laws effectively commandeer the regulatory scheme.

2. These dangers are not limited to one set of cases. As FDA has recognized, state-law claims seeking to overturn FDA's expert determinations have been brought with respect to many products and "have directly threatened the agency's ability to regulate manufacturer dissemination of risk information for prescription drugs in accordance with the act." 71 Fed. Reg. at 3934 (citing cases).

In *Dowhal* v. *SmithKline Beecham Consumer Healthcare*, 88 P.3d 1 (Cal. 2004), for example, FDA rejected a manufacturer's proposed warning on nicotine replacement therapy ("NRT") products

regarding potential birth defects or reproductive harm, as well as a citizen petition requesting additional warnings about fetal risks. *Id.* at 5-6. Nonetheless, the same individual who filed the citizen's petition also brought state-law claims against the manufacturer for failing to provide these same warnings. *See id.* at 9. Although the intermediate appellate court allowed the suit to proceed, the California Supreme Court reversed, holding federal preemption barred the claims given

> the FDA[-approved] warning serv[ed] a nuanced goal—to inform women of the risks of NRT products, but in a way that will not lead some women, overly concerned about those risks, to continue smoking. This creates a conflict with the state's more single-minded goal of informing the consumer of the risks.

Id. at 15.

Had the claims been permitted, as the lower court allowed, FDA's expert determination about what warning was required (and prohibited) under federal law could not be reconciled with a verdict for the plaintiff. The defendant would have faced impossible decisions about how to market its product: the warning required by state law would require it to violate federal law, contrary to the "nuanced goals" reflected in the agency's decision.

III. "REGULATING" DRUG LABELING THROUGH STATE LAW UNDERMINES THE PURPOSES OF THE FDCA AND HARMS PUBLIC HEALTH.

In addition to undermining FDA's judgment in a particular case and leaving regulated entities in an untenable position about whether to follow conflicting federal or state law, state-law efforts to impose

liability have a number of negative effects on federal public health objectives. These effects include: irrational prescribing due to defensive labeling, decreased innovation, decreased availability of existing treatments, and increased price.

1. First, FDA has recognized that state law liability for failure to warn creates an incentive for drug companies to engage in "'defensive labeling.'" 71 Fed. Reg. at 3934-35 (such lawsuits "can lead to labeling that does not accurately portray a product's risks, thereby potentially discouraging safe and effective use of approved products or encouraging inappropriate use and undermining the objectives of [the FDCA]"); accord Br. *Amicus Curiae* U.S. at *25-26, *Horn* v. *Thoratec* (filed 3d Cir. May 14, 2004) ("*Horn* Br."), *available at* 2004 WL 1143720. Defensive labeling can include unwarranted contraindications, as the plaintiff sought in this case, as well as other risk-adverse information and "scientifically unsubstantiated warnings," which cause physicians to misapprehend the relationship "of benefits and risks" that they rely on "to make appropriate judgments about drug use." 71 Fed. Reg. at 3935. As a result, beneficial drugs may be underutilized out of unwarranted fears or may be used when they should not be because physicians cannot distinguish the defensive labeling from the unsubstantiated risks. See *id.*; *Horn* Br., at *25-26; see generally W. Kip Viscusi, *Individual Rationality, Hazard Warnings, and the Foundations of Tort Law*, 48 Rutgers L. Rev. 625, 665-66 (1996) ("Excessive warnings are not innocuous. . . . [I]f warnings are included for inconsequential risks, they will serve to further dilute the warnings for the real hazards that should be identified to consumers.").

Crowding the warning label with a cacophony of unsubstantiated risk information also is directly contrary to regulations promulgated by FDA in 2006 which sought to make labeling easier for prescribers to understand by highlighting what the agency determines is the most important risk information. See 21 C.F.R. § 201.57(a) (discussing "Highlights of Prescribing Information" section of labeling). The Highlights section includes the most important risk information and, by design, excludes less important risk information. Highlights includes, for example, "[a] concise summary of the most clinically significant [risk] information" and recommendations for patient monitoring and other "measures that can be taken to prevent or mitigate harm." *Id.* § 201.57(a)(10); see *id.* § 201.57(a)(11) (requiring "[a] list of the most frequently occurring adverse reactions").

As FDA recognized when the Highlights regulation was issued, "[p]hysicians, pharmacists, other health care practitioners, health care advocacy groups, and professional societies and organizations representing health care practitioners expressed unequivocal enthusiasm about and uniform support for Highlights." 71 Fed. Reg. at 3930. Although FDA concluded that this provision "is a vital component of the efforts to reduce the numbers of adverse reactions from medication errors due to misunderstood or incorrectly applied drug information," the proliferation of defensive labeling would erode those advances, and thus harm FDA's core public health mission. *Id.* at 3931.

Thus, even where FDA exercises the utmost care in attempting to balance patient safety while encouraging necessary use of beneficial medications, heightened warnings may have unintended adverse consequences. In a situation where warnings above

and beyond those desired by FDA are being issued, the negative consequences of overdeterrence should be expected to increase.

2. Second, state tort liability encourages companies to halt development of promising new products. This consequence of the current liability situation clashes with a central aspect of FDA's mission: to encourage development of innovative drugs.

If state law imposes substantial liability on a manufacturer for doing just what FDA commanded it to do—as the court below allowed here—there is a perverse incentive for the manufacturer to cease innovation, particularly for drugs that are the least profitable or pose the highest degree of risk. See, *e.g.*, *Browning Ferris Indus. of Vt., Inc.* v. *Kelco Disposal, Inc.*, 492 U.S. 257, 282 (1989) (O'Connor, J., concurring in part and dissenting in part) (observing that "threat of . . . enormous awards" has convinced prescription drug manufacturers "that it is better to avoid uncertain liability than to introduce a new pill"); *Carlin* v. *Superior Court*, 920 P.2d 1347, 1361 (Cal. 1996) ("the imposition of excessive liability on prescription drug manufacturers may discourage the development and availability of life-sustaining and lifesaving drugs"). Absent preemption of appropriate claims, drug companies are left with few choices about how to structure their conduct to avoid liability. See Margaret Gilhooley, *Innovative Drugs, Products Liability, Regulatory Compliance, and Patient Choice*, 24 Seton Hall L. Rev. 1481, 1483-84 (1994) ("[M]edical experts have expressed concern that *uncertain liability standards*, coupled with litigation costs, may discourage useful drug innovation.") (emphasis added).

The easiest way to prevent unwarranted litigation may be to avoid market participation altogether, except where the potential benefits are massive. See FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (Mar. 2004), *available at* http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html ("[I]nnovators often concentrate their efforts on products with potentially high market return."); Michael Freedman, *The Tort Mess*, Forbes, May 13, 2002, *available at* http://www.forbes.com/forbes/2002/0513/090.html ("[D]rug companies are willing to take on the risk of lawsuits in marketing blockbusters . . . . [,] [b]ut in other cases the chance of liability is too great. . . . Companies also limit research on orphan drugs—those that cure rare, often fatal illnesses—because the potential tort liability outweighs the profit potential.").

3. Similarly, the threat of state-law liability for complying with FDA's determinations creates incentives for manufacturers to restrict drug uses or to withdraw approved drugs from the market. See, *e.g.*, Howard A. Denemark, *Improving Litigation Against Drug Manufacturers for Failure to Warn Against Possible Side-effects: Keeping Dubious Lawsuits from Driving Good Drugs Off the Market*, 40 Case W. Res. L. Rev. 413, 413 (1989-90) ("Beneficial drugs, approved by [FDA], have been forced off the market by the current legal standards for imposing a duty on drug manufacturers to warn of adverse side-effects from their drugs.") (emphasis omitted).

This phenomenon has been observed, for example, in the area of reproductive health. See S. Rep. No. 105-32, at 7 (1997) ("'Liability concerns are keeping products, which have already been developed, off the market despite a known therapeutic need.'") (citation

omitted). In perhaps the most famous example, Bendectin, the only FDA-approved medication for treating morning sickness, was beset by thousands of tort suits alleging birth defects even though no scientifically reliable study ever validated this connection, and FDA formally determined that Bendectin did not present this risk. See Louis Lasagna, *The Chilling Effect of Product Liability on New Drug Developments*, *in The Liability Maze* 334, 337-41 (P.W. Huber & R.E. Litan eds., 1991); FDA, Determination that Bendectin Was Not Withdrawn From Sale For Reasons of Safety or Effectiveness, 64 Fed. Reg. 43,190 (Aug. 9, 1999); *Daubert* v. *Merrell Dow Pharms., Inc.*, 509 U.S. 579, 582 (1993). Nonetheless, liability fears, litigation, and insurance costs prompted the manufacturer to withdraw the drug from the United States market—even though it still is available abroad. See generally Lasagna, *supra*, at 340-41. No substitute has since been developed or FDA-approved, leaving a treatment gap for a serious condition and triggering a substantial increase in related hospitalizations. See *id.*; Jane E. Henney, FDA/NIH Conference, *Clinical Pharmacology During Pregnancy: Addressing Clinical Needs Through Science* (Dec. 4, 2000), *available at* http://www.fda.gov/oc/speeches/2000/nichconference12-4.html.

The birth control drug Norplant also was impacted by the threat of state-law claims. See generally Anna Birenbaum, Note, *Shielding the Masses: How Litigation Changed the Face of Birth Control*, 10 S. Cal. Rev. L. & Women's Stud. 411, 412-13 (2001). Although FDA had found the drug safe and effective and it had millions of users, litigation concerns knocked the drug off the market. See *id.* Women had one less birth control option and companies were

deterred from researching and developing similar products. *Id.* at 413 ("[T]here is no longer an incentive for drug companies to research and market new birth control devices, since the threat of litigation is something that they are keenly aware of in the wake of Norplant."); see generally S. Rep. No. 105-32, at 7 ("'[l]iability concerns are stifling research and development of products for women'") (alteration in original).

4. Finally, even for drugs that make it to and remain on the market, higher prices may be the natural outcome. See, *e.g.*, *Brown* v. *Superior Court*, 751 P.2d 470, 478 (Cal. 1988) (observing that "the consuming public . . . will pay a higher price for the product to reflect the increased expense of insurance to the manufacturer resulting from its greater exposure to liability"); S. Rep. No. 105-32, at 3 ("Increased product liability costs are reflected in dramatic increases in liability insurance costs. Over the last forty years, general liability insurance costs have increased at over four times the rate of growth of the national economy."). Where liability is imposed despite a drug meeting federal standards, the resulting "product price may reflect external costs not associated with the risks of the medication [and] distort the cost-benefit calculus faced by each consumer." Note, *A Question of Competence: The Judicial Role in the Regulation of Pharmaceuticals*, 103 Harv. L. Rev. 773, 780-81 (1990).

Absent preemption, there is a substantial risk of these adverse consequences, each of which would be contrary to the FDCA's purposes.

CONCLUSION

For these reasons, and those stated in petitioner's brief, the judgment of the Vermont Supreme Court should be reversed.

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